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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 10/056,528	Applicant(s) HOCHMAN, DARYL W.	
	Examiner Brian S Kwon	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's canceling of claims 1-20 and adding claims 21-40 by Preliminary Amendment filed on 7/17/2003. Since newly added claims are aligned with the originally elected invention of Group I (claims 1-15), drawn to a process of use, claims 21-40 will be examined for prosecution on the merits.

Priority

2. Acknowledgement is made of applicant's filing of this instant application as a CIP (Continuation-In-Part) of US Application No. 09/470,637 filed 12/22/1999, now patented US Patent No. 6,495,601, which claims benefit of US Provisional Application No. 60/113,620 filed 12/23/1998. Also acknowledgment is made of applicant's claim for domestic priority of US Provisional Application No. 60/263,830 filed 01/23/2001 under 35 USC 119(e).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of migraine headache, cortical spreading depression and symptoms of migraine headache such as "visual aura", does not reasonably provide enablement for "preventing migraine headaches, cortical spreading depression and other headache conditions and symptoms of such conditions" in mammals. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: 1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

Nature of the Invention: All rejected claims are drawn to method of "preventing migraine headache, cortical spreading depression and other headache conditions and symptoms of such conditions" in subjects with the administration of the instant composition.

State of the Art: The state of the art does not recognize the administration of compositions to prevent the disorders as required in the instant claims. For instance, the state of the art recognizes the treatment of migraine headache or the treatment of migraine headache by reducing the intensity, duration, and frequency of episodes but not their cure or total eradication. The true fact of the state of art is expressed succinctly in Cady et al. ("Strategies For Optimizing Migraine Management, Proceedings From A CME Teleconference Series, September 10-14, 2001, pages 1-26, especially page 8, para. 5) and "The Migraineur's Guide to Migraine, http://www.headachecare.com".

Relative Skill of Those in the Art: The relative skill of those in the pharmaceutical art in migraine and other headaches therapy art or the migraine headache therapy art is high.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to completely eliminating or preventing claimed diseases or conditions in mammals with the administration of the instant composition makes practicing the claimed invention unpredictable in terms of the prevention of the diseases or conditions.

Breadth of Claims: The claims are very broad due to plethora of compounds having "ion-dependent cotransporter antagonist activity to the central nervous system'. Furthermore, the claim encompasses prevention of not only "migraine headaches and cortical spreading depression", but also "other headache" that may have potential causes other than those disclosed in the specification. This may or may not be addressed by the administration of the composition. Tension-type headache, cluster headache, headache associated with head trauma, vascular disorders, non-vascular intracranial disorder, substances or their withdrawal, non-cephalic infections and metabolic disorders, cranial neuralgias, nerve trunk pain and deafferentiation pain, headache due to other structure lesions, non-classifiable headache, chronic paroxysmal hemicrania and miscellaneous headaches unassociated with structural lesions are encompassed by the instant claims.

Guidance of the Specification: The instant specification provides no evidence that the claimed conditions can be prevented or completely eliminated.

The Presence or Absence of Working Examples: The instant specification discloses that (i) furosemide inhibits regenerative cortical spreading depression (page 5, lines 13-15); (ii) there is a possible link between migraine headache and indiopathic intracranial hypertension (page 5, lines 21-23); and (iii) furosemide may abort symptom of migraine headache such as visual auras by inhibiting cortical spreading depression (page 5, lines 23-25).

The Amount of Experimentation Necessary: As stated above, the art does not teach total elimination or prevention of these conditions. Therefore, the practitioner would turn to trial and error experimentation to make/use the instant compositions for "preventing migraine headache, cortical spreading depression and other headache conditions and symptoms of such conditions" in mammals, without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

For examination purposes, the phrase "preventing" is interpreted as "treating" or "ameliorating" the instant conditions.

4. Claims 21-40 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for a treatment composition comprising furosemide, more broadly loop diuretic such as furosemide and furosemide-related compositions, does not reasonably provide enablement for the term "a treatment composition having ion-dependent cotransporter antagonist activity" (claims 21, 24-26, 28-29), "the treatment composition comprises a loop diuretic" (claim 23), "thiazides and thiazide-like compositions" (claims 27, 34 and 38), "treatment composition has cation chloride cotransporter antagonist activity" (claims 22, 30-32), "the treatment composition has glial cell Na+K+2CL- chloride-dependent cotransporter antagonist activity" (claim 30) or "a treatment composition that modulates the synchronization of neuronal discharges in the central nervous system" (claims 35-37). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: 1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those

in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

Nature of the Invention: All rejected claims are drawn to method of preventing or treating migraine headache, cortical spreading depression and other headache conditions and/or symptoms of such conditions in subjects with the administration of the "a treatment composition having ion-dependent cotransporter antagonist activity" or "a treatment composition that modulates the synchronization of neuronal discharges in the central nervous system", more specifically, "treatment composition has cation chloride cotransporter antagonist activity", "the treatment composition comprises a loop diuretic, furosemide, furosemide-related compositions or thiazides and thiazide-like compositions" and "the treatment composition has glial cell Na+K+2CL- chloride-dependent cotransporter antagonist activity"

State of the Art: The art recognizes the treatment of migraine headache, cortical spreading depression and/or the treatment of migraine by controlling "visual aura" via administering furosemide.

Relative Skill of Those in the Art: The relative skill of the those in pharmaceutical art is high.

Predictability of the Art: The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F.

supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of preventing or treating migraine headache, cortical spreading depression and other headache conditions and/or symptoms of such conditions prior to filling of the instant invention was an unpredictable art.

Breadth of Claims: The claims are very broad due to the vast number of possible compounds of that are described as being "a treatment composition having ion-dependent cotransporter antagonist activity", "treatment composition has cation chloride cotransporter antagonist activity", "a loop diuretic", "thiazide-like compositions", "the treatment composition has glial cell Na+K+2CL- chloride-dependent cotransporter antagonist activity" or "a treatment composition that modulates the synchronization of neuronal discharges in the central nervous system". For instance, the breadth of "a treatment composition having ion-dependent cotransporter antagonist activity" encompasses any compositions or agents having antagonist

activity of Na+/HCO3- cotransporter, Na+/glucose cotransporter, Na+/bile acid cotransporter, Na+/H+ cotransporter, Na+/Pi cotransporter, Na+/myoinositol cotransporter, Na+/Sulfate cotransporter or K+Cl- cotransporter that can not determined by the skill artisan.

The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.), cert. Denied, 02 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for date in the future. (The length of the claimed peptide ranges from 7 amino acid residues to 68 amino acid residues in length. For claim 1, only 2 residues of the maximum 68 residues are disclosed. The limiting claims that limit the length of the peptide claims still claim peptides only disclose up to four amino acid resides.)

Guidance of the Specification: The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fishcher, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description

and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575.

In the instant case, given the unpredictability of the physiological or pharmaceutical activity of the claimed agent, the agent having "ion-dependent cotransporter antagonist activity", "cation chloride cotransporter antagonist activity", "glial cell Na+K+2CL- chloride-dependent cotransporter antagonist activity" or "modulates the synchronization of neuronal discharges in the central nervous system", or "a loop diuretic", "thiazide and thiazide-like compositions" in treating migraine headache, cortical spreading depression and other headache conditions and symptoms of such conditions is insufficient for enablement. The specification provides no guidance, in the way of enablement for that claimed agent other than furosemide, more broadly loop diuretic such as furosemide and furosemide-related compositions. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreschfiedl, 110 F. 2d 235, 45 USPQ 36 (CCPA 1940), vies this general rule: "it is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combination included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S.5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide

reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The Presence or Absence of Working Examples: As stated above, the instant specification only provides enabling disclosure for the activity of furosemide in inhibiting cortical spreading depression, treating migraine headache, and reducing "visual auras" of migraine (page 5, lines 1-25 of the instant specification).

The Amount of Experimentation Necessary: The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the agent having "ion-dependent cotransporter antagonist activity", "cation chloride cotransporter antagonist activity", "glial cell Na+K+2CL- chloride-dependent cotransporter antagonist activity" or "modulates the synchronization of neuronal discharges in the central nervous system", or "a loop diuretic" or "thiazide-like compositions" that would be enabled in this specification.

5. Claims 21-40 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The present claim is drawn to a method of preventing or treating migraine headaches, cortical spreading depression and other headache conditions and symptoms of such conditions with the administration of the instant composition.

The instant specification discloses that (i) furosemide inhibits regenerative cortical spreading depression (page 5, lines 13-15); (ii) the combination of antimigraine agents (e.g., sumatriptan, ergotamine and DHE) and medication to reduce increased intracranial pressure (e.g., acetazolamide and furosemide) is effective in reducing migraine type of chronic daily headache, suggesting a possible link between migraine headache and indiopathic intracranial hypertension (page 5, lines 21-23); and (iii) furosemide may abort symptom of migraine headache such as visual auras by inhibiting cortical spreading depression (page 5, lines 23-25). It appears in view of the instant specification that the specification is based on hypothetical theory that "spreading depression of cortical activity" may result in migraine symptoms such as "aura" of classic migraine, subsequently, the migraine headache.

As stated above, the specification discloses the activity of furosemide in (a) inhibiting regenerative cortical spreading depression, (b) reducing migraine headache and (c) treating "visual auras" of migraine, which meets the written description. However, the scope of the claimed invention encompasses other types of headaches (e.g., tension-type headache, cluster headache, headache associated with head trauma, vascular disorders, non-vascular intracranial

disorder, substances or their withdrawal, non-cephalic infections and metabolic disorders, cranial neuralgias, nerve trunk pain and deafferentiation pain, headache due to other structure lesions, non-classifiable headache, chronic paroxysmal hemicrania and miscellaneous headaches unassociated with structural lesions) and other types of symptoms of headaches (e.g., sensitivity to smell, vertigo, nausea/vomitting, depression, irritability, speech disturbances, etc...), necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. None of these meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of treatment of migraine headache, cortical spreading depression and controlling symptoms of "visual aura" of migraine, the skilled artisan cannot envision which "other headache condition and symptoms of such conditions" would be responded to activity of the claimed composition. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's

were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)* ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 21-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 35 and 38 recite a method of preventing or treating "other headache conditions" with the administration of the instant composition. The instant specification fails to

define the term. Therefore, the claims vague and unclear and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims read on a method of preventing or treating migraine headaches, cortical spreading depression and other headache conditions and symptoms of such conditions in a mammalian subject in need thereof comprising administering an effective amount of a treatment composition having ion-dependent cotransporter antagonist activity to the central nervous system of the subject. Further limitations include "cation chloride cotrasporter antagonist activity" (claim 22); "loop diuretic" (claim 23); "the subject is a human" (claims 24, 32); "a blood brain barrier permeability enhancer" (claims 25, 33, 39); "hyperosmotic agent" (claim 26); "anti-migraine agents, beta blockers, calcium channel blockers....benzodiazepines" (claim 25); "tryptans, acetaminophen, caffeine, ibuprofen....divalproex disodium" (claim 29); "glial cell Na+K+2CL- chloride-dependent cotransport antagonist activity" (claim 30); " exhibits a high degree of activity in glial cell popoulations and a lesser degree of activity in neuronal and renal cell populations" (claim 31); "a treatment composition that modulates the synchronization of neuronal discharges in the central nervous system" (claim 35); "produces diminished hypersynchronization of neuronal population activity in the central nervous system" (claim 36);

"produces modulation of the chloride concentration in extracellular space in the central nervous system" (claim 37); "formulated to facilitate crossing of the blood braine barrier" (claim 40).

7. Claims 21-23, 25-27, 30-33 and 35-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Read et al. (Cephalalgia, 1997, December, 17(8):826-832).

Read teaches the use of furosemide in saline solution, which is a loop diuretic with activity at the electroneutral Na+K+2CL-, in inhibiting regenerative cortical spreading depression in anaesthetized cats, wherein the mechanism of inhibition of cortical spreading depression activity by furosemide may be through alterations in cortical ion buffering capacity or inhibition of cell swelling in neurons or glia (abstract; page 826, column 1, para. 1-3 thru column 2, para. 1; page 837, column 2, para. 2).

Although Read is silent about the incorporation of "a blood brain barrier permeability enhancer" or hyperosmotic agent" (claims 25-26, 33 and 39); "the treatment composition exhibits a high degree of activity in glial cell popoulations and a lesser degree of activity in neuronal and renal cell populations" (claim 31); "a treatment composition that modulates the synchronization of neuronal discharges in the central nervous system" (claim 35); "the treatment composition produces diminished hypersynchronization of neuronal population activity in the central nervous system" (claim 36); "the treatment composition produces modulation of the chloride concentration in extracellular space in the central nervous system" (claim 37); and "the treatment composition is formulated to facilitate crossing of the blood brain barrier", such characteristics or properties deems to be inherent to the referenced administration of furosemide

in saline solution for inhibiting cortical spreading depression. Therefore, the reference anticipates the claimed invention.

8. Claims 21-24, 27-32 and 35-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Mathew et al. (Neruology, 1996;46:1226-1230).

Mathew the use of acetazolamide and furosemide in combination with abortive antimigraine agents (e.g., ergotamine, DHE, or sumatriptan) and prophylactic agents such as beta blockers, amitriptyline or methysergide for the treatment of chronic daily headache including migraine headache in human (abstract; page 1226, column 2, para. 5 thru page 1228, column 1, para. 1 ; page 1228, column 2, para. 6 thru page 1229, column 1, para. 1). The reference discloses that said combination resulted "in the number of days of severe headache, reduced consumption of abortive agents, and overall improvement of quality of life".

Although Mathew is silent about "the treatment composition exhibits a high degree of activity in glial cell popoulations and a lesser degree of activity in neuronal and renal cell populations" (claim 31); "a treatment composition that modulates the synchronization of neuronal discharges in the central nervous system" (claim 35); "the treatment composition produces diminished hypersynchronization of neuronal population activity in the central nervous system" (claim 36); and "the treatment composition produces modulation of the chloride concentration in extracellular space in the central nervous system" (claim 37), such characteristics or properties deems to be inherent to the referenced administration of furosemide in saline solution for inhibiting cortical spreading depression. Therefore, the reference anticipates the claimed invention.

Since the scope of instantly claimed invention encompasses the combination therapy (either coadministration or separate administration), the referenced administration of the acetazolamide and furosemide in combination with the antimigraine agents for the treatment of migraine headache by "reducing the number of days of severe headache...overall improvement of quality of life" anticipates the claimed invention.

Conclusion

9. No Claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (703) 308-5377. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax number for this Group is (703) 308-4556.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brian Kwon

ZOHREH FAY
PRIMARY EXAMINER
GROUP 1600